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Clinical Study

Lipid Lowering Therapy with Combination of Niacin and Statin in Women: Age-Related Endothelial Effects

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Background. Many women remain at risk for cardiac events despite treatment to reduce low-density lipoprotein cholesterol (LDL-C). We hypothesized that for postmenopausal women treated with niacin in addition to statin vascular function will improve. *Methods*. We conducted a randomized, double-blind, placebo-controlled trial of 16 weeks of niacin (N) versus placebo (PL) in 43 women (mean age, 67 ± 9 years) previously on statin therapy. Study outcomes included lipoprotein levels, vascular inflammation assessed by high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and endothelial function, assessed as brachial artery flow mediated dilation (FMD). *Results*. The N group significantly increased HDL-C and decreased LDL-C cholesterol relative to PL (both $P < 0.01$). FMD improved in both groups ($P = 0.02$) irrespective of niacin ($P = 0.21$). Age influenced change in FMD ($P = 0.01$) such that improved FMD (before to after) with lipid lowering therapy was greater with older age ($P = 0.03$ Pearson correlation = 0.34), independent of treatment group. *Conclusions*. Lipid lowering therapy with combination of niacin and statin does not improve inflammation or endothelial function compared to statin alone. However, older women demonstrate relatively greater endothelial benefit of lipid lowering therapy over 4 months. This trial is registered with Clinicaltrials.gov NCT00590629.

1. Introduction

Cardiovascular disease (CVD) remains the most common cause of death in women, yet our current fund of CVD knowledge in women is relatively limited [1]. While total cholesterol and LDL-C cholesterol (LDL-C) have the same risk potency for CVD among women and men, women face a relatively higher risk associated with elevated triglycerides, compared to men [2–5]. Lipid modification, primarily in the form of LDL-C lowering, has been demonstrated to result in significant 30% reduction in cardiac events [6, 7], although possibly with relatively less benefit in women [8]. A majority of women and men remain at risk for cardiac events despite LDL-C lowering, indicating that additional opportunities for risk reduction exist.

Recent evidence suggests that additional lipid fractions, specifically high levels of small dense LDL-C, triglycerides, very-low-density lipoprotein cholesterol (VLDL-C), and low HDL-C identify a group at risk for progression of atherosclerosis and future cardiac events [9–12]. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated that HDL-C elevation via the use of gemfibrozil resulted in a significant 25% reduction in the combined events of death and myocardial infarction (MI) in men with coronary disease and modest elevations in LDL-C [13]. It is notable that a major effect of gemfibrozil and niacin is to lower small, dense LDL-C, triglycerides, and VLDL-C, as well as raising HDL-C. Unfortunately, the VA-HIT trial included only men. Previous randomized controlled trial data in the Familial Atherosclerosis Treatment Study (FATS) also showed that the combination of niacin and cholestyramine worked as well as or better than lovastatin in reducing cardiac events, despite a smaller LDL-C reduction in the former group [14]. In addition, the HDL-C-Atherosclerosis Treatment Study (HATS)

demonstrated a greater than 60% risk reduction among patients randomized to simvastatin and niacin, compared to only 30% risk reduction in patients on simvastatin alone, controlling for similar LDL-C lowering [15]. By contrast, however, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, which investigated the effect of extended-release niacin in addition to simvastatin on reducing cardiovascular event incidence in patients with CVD and LDL-C cholesterol <70 mg/dL, was stopped early due to lack of efficacy of the niacin treatment [16]. Again, however, AIM-HIGH enrolled predominantly men (85% study population) and thus gender differences in cardiovascular disease, response to lipid-lowering therapy, and associated risk factors may limit generalizability of findings to women [17].

The purpose of the current study was therefore to investigate the effect of combined HDL-C elevation, triglyceride lowering, and further LDL-C reduction accomplished by the addition of niacin to statin medication as compared to LDL-C reduction alone in women with or at risk for CVD and the effect of the combination of low HDL-C/high triglycerides on endothelial function and inflammatory biomarkers. We hypothesized that the niacin plus statin regimen would beneficially improve these CVD biomarkers relative to statin therapy alone.

2. Methods

2.1. Study Design and Population. The study was a randomized, double-blind, placebo controlled trial. Stable women with or at risk for CVD on the basis of at least one cardiac risk factor were included in this study, on statin therapy with LDL-C between 90 and 135 mg/dL and triglycerides of higher than 150 mg/dL.

Women were excluded from participating in this study if they had a history of recent MI, percutaneous coronary intervention (PCI) or bypass surgery (within previous 3 months), currently on niacin therapy or unwilling to withdraw niacin therapy or known intolerance to niacin, active or known reflux disease, history of gout or on suppressive therapy, pregnant or nursing women, significant comorbidity that precludes participation or the principal investigator perceived inability to comply with the protocol, significant liver disease, active alcoholism, or liver function tests (LFT) >1.5 times upper normal limits at screening, or diabetes or glucose >126 mg/dL at screening. Concomitant medications known to increase the risk of myopathy were excluded as were other lipid modifying drugs such as fibrates. The protocol was approved by the institutional review board and all participants provided written informed consent.

2.2. Study Protocol. Eligible women were randomized to receive extended release niacin (Niaspan) (N) 1.5 g every day versus placebo (PL) in addition to usual care statin lipid-lowering agents. The extended release niacin dose was titrated over a 4-week period and patients remained on the study drug for 12 more weeks, for a total of 16 weeks on extended release niacin or placebo. An unblinded study physician adjusted the statin doses in both placebo and niacin arms at week 10 of the 16-week period in order to maintain similar LDL-C levels of less than 100 mg/dL.

2.3. Interventions. Participants were randomly assigned to receive N or PL for 16 weeks.

2.4. Blood Testing. Levels of plasma total cholesterol, high-density lipoprotein cholesterol HDL-C, LDL-C and VLDL-C, and triglycerides were measured as previously published [18]. Plasma glucose, HgA1C, LFTs, CPK, and inflammatory markers high sensitivity C-reactive protein (hsCRP), Interleukin 6 (IL-6), Tumor Necrosis Factor α (TNF-α) were also measured. All samples were analyzed at the Core Laboratory at Harbor UCLA Medical Center, Los Angeles, CA. Enzymatic methods were used to determine the concentrations of total cholesterol and HDL-C after dextran sulfate precipitation.

2.5. Brachial Artery FMD Protocol. Details of the FMD protocol used have been described in a previous report [19, 20]. In brief, patients were instructed to fast overnight and withdraw from vasoactive medication 24 to 48 hours prior to the test. Peripheral flow-mediated, endothelium-dependent vasomotion (FMD) and endothelium-independent vasodilation with nitroglycerine (NTG) in the brachial artery were examined using a high-resolution B-model ultrasonography technique [21] and validated analytical methods [22] were used to measure FMD.

2.6. Statistical Analysis. Descriptive statistics were used to summarize the entry characteristics of study participants. For all analyses, the subjects were divided into 2 groups: N versus PL. Variables of interest at baseline and after 16 weeks in each group were compared with each other. Frequency distributions were generated for categorical variables and means, medians, and standard deviations were computed for continuous variables. Baseline comparisons between the two groups were performed by the unpaired t-test for normally distributed continuous measures, by the Wilcoxon rank-sum test for abnormally distributed continuous measures and by the chi-square test or Fisher's exact test for discrete variables. A repeated measures model was used to examine differences in continuous measures between study entry and exit with time as the within-subjects factor, group as the between-subjects factor, the group by time interaction to explore a treatment effect, and relevant continuous variables included as covariates. Multivariable regression was performed using the method of least squares to fit general linear models, adjusting for covariates as appropriate. A P value of 0.05 was required for statistical significance. All analyses were conducted using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

Baseline characteristics of the two groups are compared in Table 1. The mean age of the participants was 66.7 years; 86% were Caucasian and more than half had completed college.

Table 1: Clinical characteristics and medications, by intervention group*.

Variables^ (visit)	Category	Niacin plus statin group	Placebo plus statin group	*P* value
Age (yr)				
Mean (SD)		67.73 (11.27)	65.62 (6.40)	0.45
Median		68.50	66.00	
Completed study	Yes	16 (72.73)	20 (95.24)	0.10
	No	6 (27.27)	1 (4.76)	
Relatives with CHD	Yes	11 (55)	9 (50)	0.76
	No	9 (45)	9 (50)	
High blood pressure (ever told)				
Entry (visit 2)	Yes	15 (68.2)	12 (57.1)	0.45
	No	7 (31.8)	9 (42.9)	
Diabetes (ever told)				
Entry (visit 2)	Yes	2 (9.1)	1 (5.0)	1.00
	No	20 (90.9)	19 (95.0)	
Stroke	Yes	2 (9.1)	1 (4.76)	1.00
	No	20 (90.9)	20 (95.24)	
Smoking	Current	1 (4.5)	2 (9.52)	0.24
	Past	7 (31.82)	11 (52.38)	
	Never	14 (63.64)	8 (38.10)	

^Unless otherwise indicated, data are expressed as number (percentage of treatment population).
*For the niacin group $n = 22$, placebo group = 21, at entry. Six patients in the niacin group and 1 patient in the placebo group did not complete the study.
Yr: years; SD: standard deviation; CHD: coronary heart disease; *P* value represents between-group comparison.

No major differences in clinical characteristics were detected between the two groups at study entry.

3.1. Study Outcomes

3.1.1. Tolerability and Safety. A total of 43 women were enrolled in the study protocol. Seven patients did not complete the study, six of whom were assigned to receive N. The difference was almost entirely accounted for by flushing or other cutaneous reactions. No drug-related myopathy was observed; no patient had elevated creatine kinase or LFT that precluded staying in the study. One patient receiving statin alone was diagnosed with a deep venous thrombosis during the intervention period. The patients who dropped out of the study did not differ from the patients who completed the study in any baseline characteristic (all $P > 0.18$) except for NTG dilation (9.0 ± 5.3% in dropouts versus 14.8 ± 6.3% in completers; $P = 0.04$).

3.1.2. Lipoprotein and Inflammatory Biomarker Changes. Significant differences between the two groups in exit HDL-C and LDL-C were observed (Table 2), with changes in triglycerides, HDL-C, and LDL-C before and after the study observed among patients in the N but not the PL group. There were no group differences or changes before and after the study in hsCRP, IL-6, or TNF-α (Table 2).

3.1.3. Brachial Artery FMD. There was a significant group difference in FMD ($P = 0.01$) such that the placebo group had higher FMD at both pre- and poststudy timepoints. In addition, FMD increased similarly across time ($P = 0.02$) in both groups (Figure 1) with no additive influence of niacin treatment ($P = 0.21$). Age was significantly associated over time with FMD ($P = 0.01$) such that the improvement in FMD during the study with lipid lowering therapy was greater

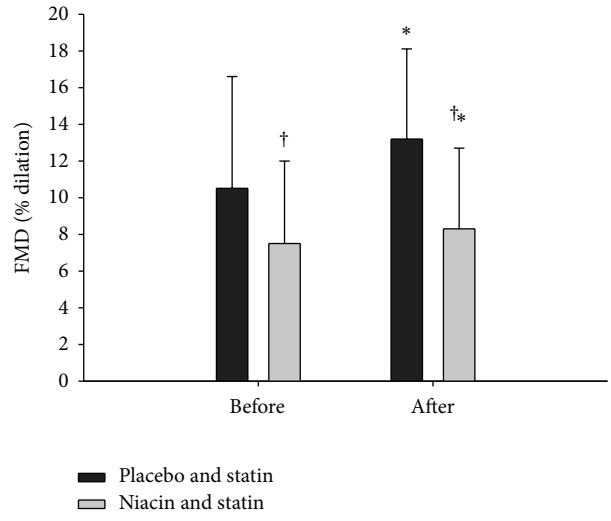

Figure 1: Group means (±standard deviation) of brachial artery FMD before and after treatment with statin therapy and placebo (black bars) versus combined niacin and statin therapy (grey bars). *: indicates a significant ($P < 0.05$) difference from baseline within a group and †indicates a significant ($P < 0.05$) difference between groups at a timepoint.

Table 2

Variable	Visit	Niacin plus statin group	Placebo plus statin group
TC (mg/dL)	Entry	191.1 (17.1)	202.5 (31.0)
	Exit	188.9 (20.3)	198.4 (26.9)
LDL-C-C (mg/dL)	Entry	100.6 (15.2)	113.0 (28.1)
	Exit	84.8 (18.0)*	105.6 (17.5)†
HDL-C-C (mg/dL)	Entry	55.5 (10.3)	59.5 (12.2)
	Exit	75.4 (18.9)*	60.3 (11.6)†
TG (mg/dL)	Entry	174.7 (85.1)	150.2 (71.4)
	Exit	144.6 (75.32)*	162.8 (73.4)
IL-6 (pg/mL)	Entry	1.69 (0.53)	2.68 (4.17)
	Exit	2.11 (0.84)	2.66 (4.33)
TNF-α (pg/mL)	Entry	2.30 (0.86)	2.97 (3.68)
	Exit	3.91 (4.32)	3.11 (3.21)
hsCRP (mg/L)	Entry	4.11 (2.96)	3.99 (3.69)
	Exit	4.28 (3.88)	4.71 (6.23)

Data shown as group means (standard deviation). *Significant ($P < 0.05$) change within a group between entry and exit; †Significant ($P < 0.05$) difference between groups at exit.
TC: total cholesterol; LDL-C-C: low-density lipoprotein cholesterol; HDL-C-C: high-density lipoprotein cholesterol; TG: triglycerides; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; hsCRP: high sensitivity C-reactive protein.

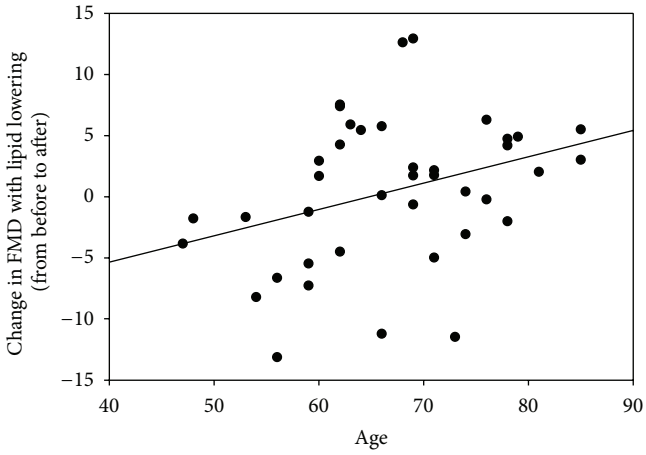

Figure 2: Individual datapoints with regression line showing the relationship between the change in FMD (before and after treatment measurements) and age.

with increasing age (Figure 2). However, changes in lipids before and after the study (HDL-C, LDL-C, VLDL-C, TC, and TG) were not associated over time with FMD (all $P > 0.43$). In addition, neither there was a group difference in endothelium-independent dilation ($P = 0.09$) nor it changed over the course of the study in all subjects ($P = 0.76$) or by group (PL NTG before to after: 16.7 ± 8.5% to 18.8 ± 5.7%; N before to after: 13.9 ± 5.6% to 14.1 ± 5.0%; $P = 0.09$).

4. Discussion

Results from the current study demonstrate a lipid-modifying effect of 1500 mg extended release niacin plus statin that is consistent with the magnitude of effect reported in the literature [23–25] for niacin. Overall, we observed a modest reduction in triglycerides of 17% with the combination, a favorable 36% elevation of HDL-C cholesterol, and a 16% reduction in LDL-C. The regimen was generally well-tolerated although we observed more discontinuation for flushing and other cutaneous reactions in the niacin plus statin group, consistent with previous studies [26]. Notably, despite these lipoprotein changes, there were no group differences in markers of endothelial function and/or inflammation (FMD, hsCRP, IL-6, or TNF-α) at study exit. These findings are notable in light of the early discontinuation of the AIM-HIGH study where, despite significant increases in HDL-C cholesterol and decreases in triglyceride levels, study patients exhibited no significant reduction in the primary composite end point of cardiovascular events over a mean follow-up period of 36 months [16]. Therefore, these current data may provide preliminary mechanistic understanding of the failure of niacin plus statin to improve cardiovascular outcomes in a large scale clinical trial relative to statin therapy alone.

In addition, we observed a significant relation between FMD and age. Specifically, improved FMD (before to after) during the trial was evident among older age subjects, independent of treatment group. This effect persisted even when the model was adjusted for relevant covariates. Endothelial function is a major contributor to coronary disease pathophysiology [27, 28]. We as well as others have previously demonstrated that lowering LDL-C levels significantly improves endothelial function as measured by brachial artery reactivity [19] Several recent meta-analyses regarding sex differences in efficacy of statin therapy for reducing primary and secondary cardiovascular events demonstrate a statistically significant benefit of statin therapy in women [8, 29]; however, the relative benefit may be less in women than men for primary prevention. Consequently the current

results provide a potential mechanistic understanding of these outcome study results, finding that endothelial function is relatively more improved in older women. Interestingly, changes in lipids themselves did not significantly influence the increase in FMD over time, possibly because women were already on statin therapy prior to enrolling in the trial. Consequently, work in a larger study group is needed to better understand the relationship between age, statin therapy, and endothelial function.

Previous work has demonstrated that HDL-C is also a significant mediator of endothelial function, as measured in both the coronary and brachial arteries [30, 31]. Moreover, in several studies administering niacin to patients with low HDL-C, improvements in brachial or radial artery endothelial function have been observed [32, 33] although this improvement has not been observed following augmentation of HDL-C with the cholesterol ester transfer protein inhibitor JTT-705 [34]. To the best of our knowledge, the current study is the first to investigate the effect of HDL-C raising specifically on endothelial function in women. The mechanism underlying lack of any additional improvement in brachial artery FMD with niacin plus statin compared to statin alone is unclear. One possibility is that the pathways underlying the improvement in FMD with statin therapy, which include reduction of acetylcholine-induced vasoconstriction or augmented peripheral NO-mediated vascular relaxation [35], are either not affected by niacin treatment or, more plausible, are limited by a ceiling effect such that combination lipid-modifying therapy evokes no further improvement in endothelial function. This is in contrast to the effect of niacin on established atherosclerotic vascular disease; for example, in the HATS trial [15], where 160 patients with known coronary heart disease were randomized to simvastatin or to simvastatin plus niacin and followed for 2.5 years, a significant regression of coronary atherosclerosis was observed in the combination therapy group—more than twice that expected with statin therapy alone.

Study Limitations. Our study limitation is its inability to evaluate the impact of these cholesterol changes on cardiovascular endpoints. Also, we did not administer a low dose of niacin in the PL group (similar to the study design utilized in AIM-HIGH), and thus it was difficult to keep subjects blinded to their treatment group. However, given that outcome measurements were objective biomarkers of endothelial, lipid, and inflammatory function, it is unlikely that subject-specific unblinding explains the lack of observed effect of combined lipid modifying therapy. In addition, we enrolled only women with or at CVD risk in the study, limiting generalizability of results and potentially limiting our sensitivity to detect changes in outcomes potentially observed in a more heterogeneous, healthier, or younger group. Regardless, given the equivocal data regarding efficacy of niacin treatment on cardiovascular outcomes as well as statins in older women, these results may help clinicians weigh the costs and benefits of a commonly used combined lipid-modifying treatment aimed at targeting high LDL-C and low HDL-C.

5. Conclusions

Combination therapy with niacin and statin exhibits potent synergistic actions on multiple lipid measures but does not appear to be an effective strategy for management of endothelial function and/or inflammation in women. Our observations of an age-related benefit of lipid-lowering therapy on endothelial function independent of treatment assignment support the clinical trial outcome data that relatively greater benefit of statin therapy is seen in older women. Further exploring endothelial pathways could provide insights into the therapeutic efficacy of lipid lowering therapy in older women.

Disclosure

All authors (except Dr. Paul-Labrador, who deceased and participated in data collection and analysis only) take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflict of Interests

No authors report conflict of interests, and the lead author does not have a direct financial relation with the commercial identities mentioned in the paper that might lead to a conflict of interests for any of the authors.

Authors' Contribution

Beth Parker and Kamlesh Kothawade contributed equally.

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